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A comparative analysis of changes in pMDI drug dose delivery before and after detergent coating using five antistatic valved holding chambers

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Clinical Implications

- Some “antistatic” valved holding chambers are only poorly antistatic and are, therefore, rather to be used as ordinary nonantistatic ones (eg, including “priming”). As a result, antistatic valved holding chambers are noninterchangeable, which means that switching between them should be discouraged.

TO THE EDITOR:

Pressurized metered dose inhalers (pMDIs) are preferably to be used in combination with a spacer or valved holding chamber (VHC). Most notably, this reduces the impact of actuation-inhalation (“hand-lung”) coordination problems, and it lowers oropharyngeal deposition as smaller particles are presented to the patient at a lower velocity.^{1,2} Spacers and VHCs may therefore improve compliance and reduce the chance of local and systemic side effects with the use of pMDIs.

Although the use of spacers and VHCs is warranted by the advantages they offer, they also retain a notable fraction of the drug and hence lower the dose from a pMDI that is delivered to the patient. Moreover, not only differences in the size, shape, or construction material, but also differences in the cleaning and use of spacers and VHCs may greatly affect the delivered doses from these devices and limit their interchangeability.¹ This was recently illustrated in a comparison of 4 antistatic VHCs (aVHCs) by Dissanayake et al.³ They showed that the fine particle dose from a salbutamol pMDI (Ventolin) may differ by up to a factor 2, even for VHCs that are comparable in size, shape, and (claimed) antistatic properties.

Such significant performance differences between similar aVHCs complicate the drafting of generally applicable guidelines for their choice and use. For example, nonconducting spacers and VHCs can be made “antistatic” with a detergent coating (ie, “primed”) by soaking them in a household detergent solution followed by drying to the air, also known as “drip-drying.”⁴ This lowers drug retention in the VHCs caused by electrostatic attraction. Understandably, drip-drying is only advocated for nonconducting VHCs, whereas it is deemed unnecessary for aVHCs.² However, if the great performance differences between aVHCs are caused by differences in their antistatic properties, drip-drying may be advisable for some of these devices too. Furthermore, the performance differences may then depend on the type of drug or the pMDI being used, as drugs and their

formulations may differ in their sensitivity to electrostatic charging.

To test the supposition that all aVHCs are equally antistatic and do not need to be coated with a detergent by drip-drying, we determined the delivered doses of salbutamol (Ventolin 100 µg/ dose label claim) and beclomethasone dipropionate (Qvar 100 µg/ dose label claim) from the Aerochamber Plus Flow-Vu (AC+FV), the Compact Space Chamber Plus (CSC+), the InspiraChamber (IC), the OptiChamber Diamond (OCD), and the Vortex (Vortex); see Figures E1 and E2, and Table E1 (available in this article’s Online Repository at www.jaci-inpractice.org). These aVHCs were cleaned in a mild detergent solution and either rinsed with water (to test their intrinsic antistatic properties) or “drip-dried” (to test standardized antistatic properties) before every measurement. The “rinsing” method is the cleaning method advocated by aVHC manufacturers. More methodological details about the experiment are available in this article’s Online Repository at www.jaci-inpractice.org.

The “rinsing” method causes a difference in the delivered dose between the aVHCs of up to a factor 2, with the Vortex and AC+FV performing significantly better than the CSC+, IC, and OCD (Figure 1). Drip-drying particularly increases the delivered doses from the CSC+ and the IC ($.0003 < P < .06$, Figure 1), which indicates that their antistatic properties are suboptimal. On the contrary, the antistatic properties of the AC+FV, OCD, and Vortex are optimal, as their delivered doses are minimally affected by drip-drying. The consistently lower delivered dose from the OCD than from the AC+FV and Vortex therefore must be the result of differences other than their antistatic properties, such as their size, shape, or valve functioning.

It follows from these results that differences in antistatic properties are an important cause of the large performance differences between aVHCs. Therefore, the assumption that aVHCs do not require drip-drying to improve drug delivery does not hold true for all of these devices. Furthermore, drip-drying may greatly improve the interchangeability of aVHCs, as no significant differences in delivered dose between 4 of 5 aVHCs tested (AC+FV, CSC+, IC, and Vortex) were measured after drip-drying, whereas only 2 (AC+FV and Vortex, or CSC+ and IC) performed similarly after rinsing. Therefore, as a general guideline, it seems appropriate to recommend drip-drying, even for aVHCs, or to at least discourage the switching between them.

It should be noted that a similar delivered dose in this study may not equal full *in vitro* equivalence of the devices. For that, also the particle size distributions of the delivered doses have to be identical. It is worth pointing out in this regard that the Vortex does not result in a finer aerosol of beclomethasone than the pMDI alone, contrary to the other aVHCs (see Table E2, available in this article’s Online Repository at www.jaci-inpractice.org). This may result in a different deposition pattern. Patient factors will also affect the deposition pattern, and therefore, the clinical implications of the observed differences can only be determined by *in vivo* studies. Nevertheless, a lower delivered dose with an aVHC compared with a pMDI alone does not necessarily result in a lower bioavailability,^{5,6} as the lung deposition fraction may increase.

The approximate 2-fold difference in delivered dose between salbutamol and beclomethasone when used with an aVHC can

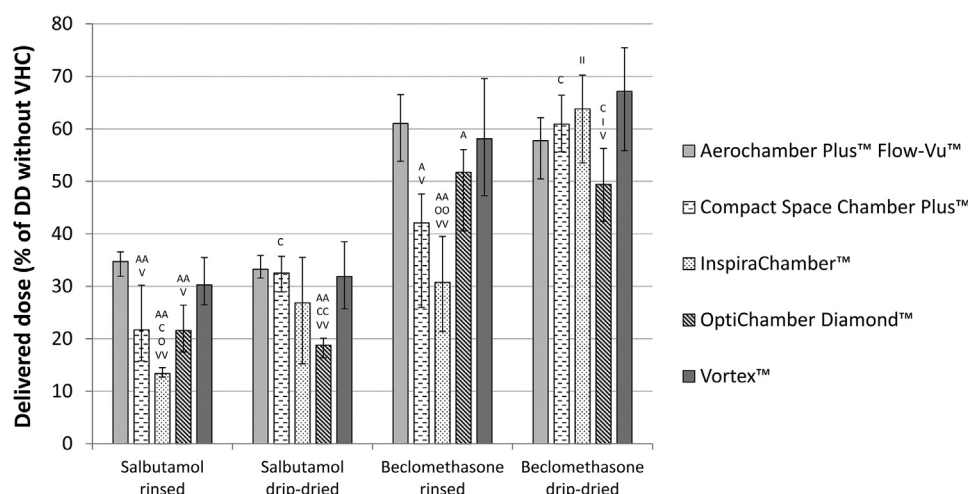


FIGURE 1. Delivered doses of salbutamol (Ventolin) and beclomethasone (Qvar) from different antistatic valved holding chambers (aVHCs) after rinsing or drip-drying. The letters denote a significant difference in the delivered dose with the corresponding aVHCs, with $P < .05$ (single letter) or $P < .005$ (double letters). Error bars represent the minimum and maximum values measured ($n \geq 4$).

be explained by their different aerosol characteristics. The salbutamol pMDI has a higher plume velocity⁷ and a larger median particle size of the aerosol than the beclomethasone pMDI (see Figure E3 and Table E2, available in this article's Online Repository at www.jaci-inpractice.org). Both factors likely increase salbutamol particle deposition in the aVHCs by inertial impaction and sedimentation.

The qualitative similarity of the results obtained with the different drugs (salbutamol and beclomethasone) from different pMDI types suggests that the findings from this study are generally applicable to other pMDIs. Despite differences in particle size distribution and aerosol plume velocity between salbutamol and beclomethasone, performance differences between the individual aVHCs remain largely the same. Also a different charging behavior of both drug products⁸ does not affect the aVHC performance differences.

The clinical benefit of spacers and VHCs is extensively discussed by others. Rather than doubting this benefit, health care workers should be aware of the far-reaching non-interchangeability of VHCs, including their antistatic counterparts. Although this noninterchangeability of VHCs is well recognized,^{1,2} aVHCs are often considered a homogeneous, interchangeable group of devices. However, this study shows that the antistatic properties of some aVHCs, such as the CSC+ and IC, are suboptimal to such an extent that they are rather to be used as ordinary nonconducting VHCs instead, and that switching between aVHCs should be discouraged.

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MATERIALS AND METHODS

Five antistatic valved holding chambers (aVHCs) of similar size and shape were obtained through a local pharmacy. These are the Aerochamber Plus Flow-Vu (AC+V), the Compact Space Chamber Plus (CSC+), the InspiraChamber (IC), the OptiChamber Diamond (OCD), and the Vortex (Vortex, Figure E1). Characteristics of these aVHCs, such as their manufacturers and dimensions, are summarized in Table E1. Because the type of drug may affect its sensitivity to static charge, a salbutamol pressurized metered dose inhaler (pMDI) (Ventolin 100 µg/dose label claim; GlaxoSmithKline, Brentford, UK) and a beclomethasone dipropionate pMDI (Qvar 100 µg/dose label claim; Teva, Petah Tikva, Israel) were used. The salbutamol pMDI contains a suspension, whereas the beclomethasone pMDI contains a solution. Each aVHC and each pMDI were tested in 4-fold ($n = 4$).

Cleaning of the aVHCs

To study whether the performance difference between the aVHCs is caused by a difference in their antistatic behavior, 2 different aVHC cleaning procedures were compared. First, the aVHCs were disassembled into their separate parts and soaked in a lukewarm mild detergent solution for 15 minutes. A normal household detergent was used in an uncontrolled concentration (roughly suitable for dishwashing), as the type and concentration of the detergent do not determine its antistatic effect.^{E1} Hereafter the parts were dried to air in vertical position either directly (ie, “drip-dried”) or after rinsing with water (ie, “rinsed”). Rinsing is instructed by the manufacturers of the aVHCs and results in testing of the aVHCs’ intrinsic antistatic properties. Drip-drying on the other hand is expected to result in a uniform detergent coating across the aVHCs, thereby giving them the same antistatic properties. Cleaning by either rinsing or drip-drying of the aVHCs was performed before each individual measurement.

Dose collection

The delivered doses from the pMDIs or the pMDI-aVHC combinations were determined with the dose collection apparatus described in the European Pharmacopoeia.^{E2} A flow rate of 30 L/minute was drawn through the apparatus for a total volume of 4 L and the aerosols were collected in glass fiber filters. The salbutamol pMDI was shaken vigorously for 5 seconds before every actuation to homogenize the suspension, whereas the beclomethasone pMDI with a solution was used without shaking. The first 10 doses, as well as every dose before a measurement, were discharged to waste to prime the pMDIs. A single measurement consisted of 10 (salbutamol) or 5 actuations (beclomethasone). A delay of at least 30 seconds between every actuation was applied to prevent the pMDI nozzles from freezing. A 2-second delay was applied between actuation of the pMDIs into an aVHC and the onset of the simulated inhalation maneuver.

The delivered dose from a pMDI may lower with increasing dose number, especially for pMDIs that contain a suspension.^{E3} To enable the correction for such a drift in delivered dose, delivered dose measurements with an aVHC were always performed in between 2 measurements with a pMDI alone. The delivered dose from the aVHC was subsequently calculated relative to the average of the delivered doses from the pMDI

alone determined directly before and after. This way, any performance variations of the pMDIs will not reflect in the performance of the aVHCs. Single measurements with all 5 aVHCs were always performed on the same day so as to minimize variation between the aVHCs due to differences in environmental conditions during the experiments.

Sample preparation and analysis

Samples were collected by rinsing the dose collection apparatus and soaking the glass fiber filter with water (salbutamol) or ethanol (beclomethasone) and consecutively passing the solutions through a 0.2-µm membrane filter to remove any suspended glass fibers. The filtrate was then analyzed spectrophotometrically at 225 (salbutamol) or 239 nm (beclomethasone) with a Unicam UV 500 (ThermoSpectronic, Cambridge, UK).

Laser diffraction analysis

The particle size distributions of the aerosols directly from the pMDIs or delivered via “rinsed” aVHCs were measured by laser diffraction analysis with the HELOS BF and INHALER 2000 adaptor (Sympatec, Clausthal Zellerfeld, Germany). A flow rate of 30 L/minute was applied by means of a venturi flow-pressure indicator. Actuation procedures for the pMDIs were as described for the determination of the delivered dose. To exclude any influence of the aerosol propellant on the particle size distributions, data of the inner 9 detector rings were excluded by means of the “forced stability” setting. Results are the average of 5 measurements ($n = 5$).

Aerosol imaging

Aerosol plumes from the salbutamol and beclomethasone pMDIs were imaged using a Phantom VEO-E 310L high-speed camera (Vision Research) equipped with a 24–85 mm lens (Nikon, Tokyo, Japan). The aerosol was lighted with a 12,000 lm led light from below. The aerosol was filmed at 240 frames per second, and the 12th frame at 0.05 seconds after first exit of the aerosol from the mouthpiece was taken for an indication about the aerosol shape and velocity.

Statistical analysis

Statistical tests were performed with Microsoft Excel 2010. Equality of variance was tested by means of the F test. Depending on the outcome of the F test, a homoscedastic or heteroscedastic 2-tailed Student’s t test was performed to determine the statistical significance of any differences in the mean delivered doses.

RESULTS

The delivered doses of the salbutamol and beclomethasone pMDIs across the dose numbers used for the experiments in this study are presented in Figure E2. Despite vigorous shaking during 5 seconds before every actuation, a drift in delivered dose with increasing dose number occurs for the suspension pMDI (salbutamol) from around 100% to 76% of the label claim. The solution pMDI (beclomethasone) on the other hand shows a trend of slightly increasing delivered dose from 71% to 79% of the label claim. The delivered dose of the beclomethasone pMDI is generally lower than that of the salbutamol pMDI, because its label claim refers to the metered (ex-valve) dose, whereas that of the salbutamol pMDI refers to the delivered (ex-mouthpiece) dose.

The data from laser diffraction analysis show that a finer aerosol is emitted from the beclomethasone pMDI than from the salbutamol pMDI with d50 values of 1.86 and 3.05 μm , respectively (Table E2). The use of an aVHC generally lowers the d50 value of the inhaled aerosols, with the exception of the Vortex aVHC in combination with the beclomethasone pMDI.

Images of the aerosols from the salbutamol and beclomethasone pMDIs after 0.05 seconds are shown in Figure E3. The

aerosol of the salbutamol pMDI exits as a jet that starts expanding only after approximately 15 cm and reaches to roughly 30 cm from the mouthpiece of the pMDI after 0.05 seconds, whereas the aerosol from the beclomethasone pMDI starts expanding within the first 10 cm and reaches to around 20 cm from the mouthpiece in the same time. The salbutamol aerosol therefore exits at a higher velocity than the beclomethasone aerosol. This is in line with the higher “plume impact force” for the salbutamol pMDI reported by Gabrio et al.^{E4}

TABLE E1. Overview and characteristics of the aVHCs tested

Valved holding chamber	Abbreviation	Manufacturer	Material	Dimensions
Aerochamber Plus Flow-Vu	AC+FV	Trudell Medical International	Charge dissipative plastic polymer	14.5 × 4.6 cm 149 mL
Compact Space Chamber Plus	CSC+	Medical Developments International	Charge dissipative plastic polymer	14.5 × NA cm 160 mL
InspiraChamber	IC	InspiRx Inc., Lupin Pharmaceuticals Inc.	Charge dissipative plastic polymer	NA
OptiChamber Diamond	OCD	Philips Respironics Inc.	Charge dissipative plastic polymer	15 × 5.5 cm 140 mL
Vortex	Vortex	PARI Respiratory Equipment, Inc.	Aluminum	15.7 × 5.4 cm NA mL

aVHC, Antistatic valved holding chamber; NA, not available.

TABLE E2. The median diameter (d50) and fine particle fraction <5 μm (FPF) determined by laser diffraction analysis for the pMDIs alone (no aVHC) and in combination with different aVHCs (n = 5)

	Salbutamol		Beclomethasone	
	d50, μm (SD)	FPF, % (SD)	d50, μm (SD)	FPF, % (SD)
No aVHC	3.05 (0.12)	86.13 (2.03)	1.86 (0.06)	98.17 (2.29)
AC+FV	2.81 (0.02)	88.94 (2.23)	1.42 (0.05)	100 (0.00)
CSC+	2.61 (0.09)	93.88 (0.82)	1.41 (0.12)	99.97 (0.07)
IC	2.75 (0.04)	91.41 (1.42)	1.43 (0.06)	100 (0.00)
OCD	2.82 (0.10)	89.63 (0.78)	1.34 (0.06)	100 (0.00)
Vortex	2.84 (0.14)	87.19 (2.61)	1.86 (0.06)	100 (0.00)

AC+FV, Aerochamber Plus Flow-Vu; aVHC, antistatic valved holding chamber; CSC+, Compact Space Chamber Plus; IC, InspiraChamber; OCD, OptiChamber Diamond; pMDI, pressurized metered dose inhaler; SD, standard deviation.

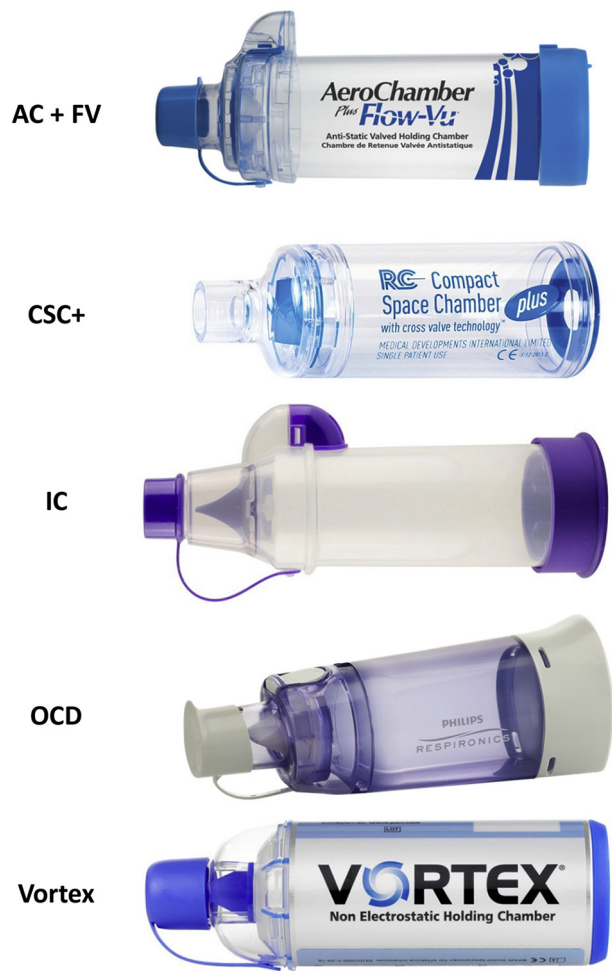


FIGURE E1. The antistatic valved holding chambers tested in this study: Aerochamber Plus Flow-Vu (AC+FV), Compact Space Chamber Plus (CSC+), InspiraChamber (IC), OptiChamber Diamond (OCD), and Vortex (Vortex).

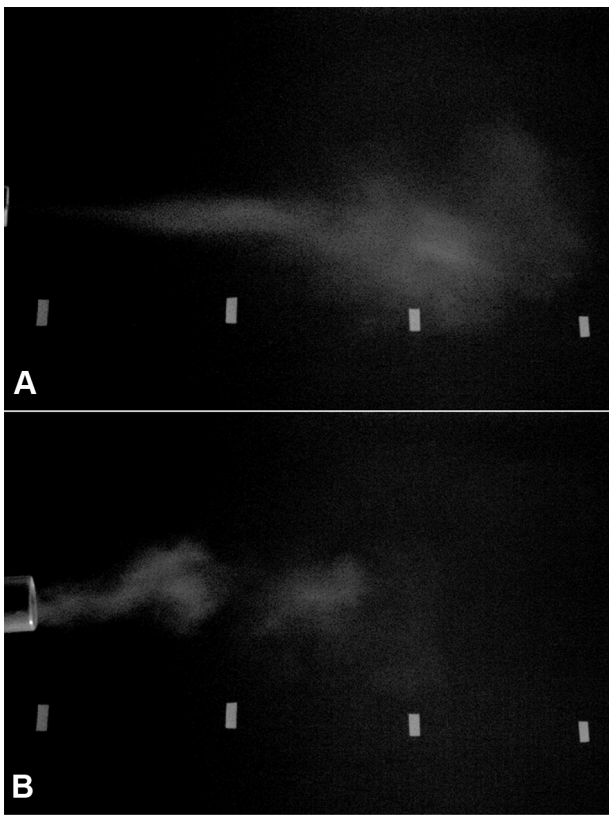


FIGURE E3. Plumes of the salbutamol pMDI (Ventolin, **A**) and beclomethasone pMDI (Qvar, **B**) imaged 0.05 seconds after emission by means of a high-speed camera. The white marks are spaced 10 cm apart (ie, a total length of approximately 30 cm from the pMDI mouthpieces is imaged). *pMDI*, Pressurized metered dose inhaler.

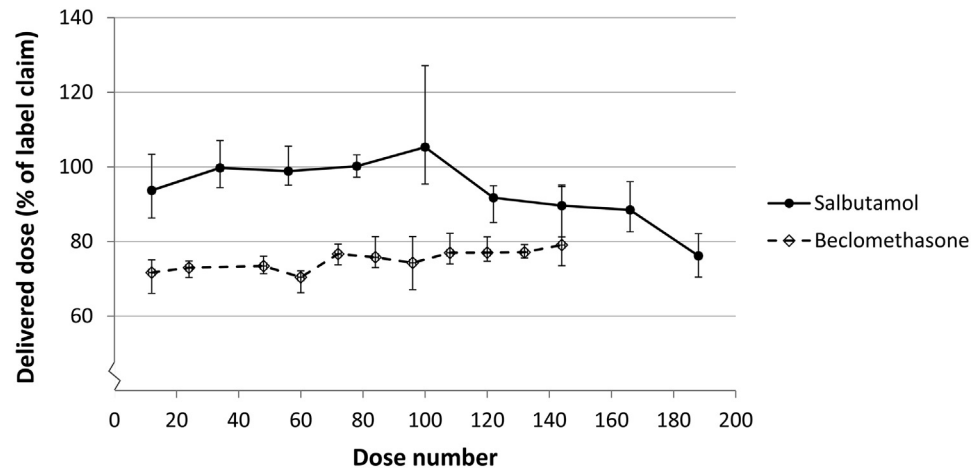


FIGURE E2. Delivered doses of salbutamol (Ventolin) and beclomethasone (Qvar) without the use of a VHC across the range of dose numbers used in this study ($n = 5$). Each experiment with an aVHC was performed in between 2 consecutive data points, after which the delivered dose from the aVHC was calculated relative to the average of these 2 points. *aVHC*, Antistatic valved holding chamber.

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